Thyroid Peroxidase Antibodies in Non-Autoimmune Hyperthyroidism Treated with Radioactive Iodine

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Abstract
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Introduction: Earlier studies suggest increased serum levels of thyroid peroxidase antibodies (TPOAb) in some cases with non-autoimmune hyperthyroidism. The aim of the study was to assess the incidence of hypothyroidism in patients with nodular toxic goitre and toxic adenoma at 12 months after radioactive iodine therapy in the relation to TPOAb levels.
Patients & Measurements: The study comprised 100 patients (83 females; 17 males) treated with radioactive iodine therapy. Serum concentrations of thyrotropin, free thyroxin, TPOAb, and anti-TSH receptor antibodies were assessed at baseline and 12 months after radioactive iodine therapy.
Results: High TPOAb level (>60.0 IU/mL) was found in 27% of patients at baseline and 32% at the follow-up. Baseline TPOAb values were higher in subjects with coexisting non-thyroid autoimmune disease (p=0.041). After radioactive iodine therapy, the mean TPOAb level increased in patients with normal baseline TPOAb (p=0.03) and the rates of euthyroidism and hypothyroidism were 61 and 34%, respectively. The rate of hypothyroidism after radioactive iodine therapy was not significantly different in groups with normal and high baseline TPOAb.
Conclusions: 27% of patients with non-autoimmune hyperthyroidism were positive for TPOAb. However, baseline TPOAb level did not influence the rate of hypothyroidism at 12 months after radioactive iodine therapy. Our results suggest a more close surveillance after radioactive iodine therapy of patients harboring these antibodies.

Introduction
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Distinguishing between autoimmune and non-autoimmune hyperthyroidism (NIH) is crucial for radioactive iodine therapy (RIT) because different approaches to patient preparation and follow-up are required [1,2]. In a typical course of NIH the medical history, thyroid hormone levels, ultra-sonographic appearance, and the thyroid scan pattern are sufficiently diagnostic but in case of uncertainty (for example of uneven distribution of ^{99m}Tc) the key point of differential diagnosis is the measurement of anti-TSH receptor antibodies (TRAb) [3,4]. The value of anti-thyroid peroxidase antibodies (TPOAb) in diagnosing of thyroid disorders is less specific. Although 90% of patients with Hashimoto's thyroiditis and 70% with Graves' disease show TPOAb positivity, a moderately increased TPOAb concentration has also been reported in 12–26% of patients with non-autoimmune thyroid goitre or autonomous thyroid disease and euthyroid adults in the age-dependent patterns [5–7]. It is generally believed that TPOAb positivity in euthyroid subjects is predictive for clinical and subclinical chronic autoimmune thyroiditis and subsequent hypothyroidism [7–13]. There is a limited number of studies which deal with the problem of elevated TPOAb levels in NIH treated with RIT, and they yielded inconsistent results. While Pisarek et al. [14] found no association of post-RIT hypothyroidism in patients with baseline elevated TPOAb, Carceler et al. [15] and Bolusani et al. [16] found the increased risk of hypothyroidism in these cases. In this study, we evaluated the incidence of hypothyroidism in patients with nodular toxic goitre and toxic adenoma at 12 months after RIT in the relation to baseline TPOAb levels.

Material and Methods
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Patients
The study group comprised 100 consecutive patients (83 women, 17 men) aged 65.0±11.9 years (range 33–90 years) with toxic multinodu-

lar goitre (MNTG; n=65) and toxic adenoma (TA; n=35) who were referred for RIT to the Department of Nuclear Medicine between January 2010 and March 2011 inclusive. MNTG was defined as a thyroid gland with 2 or more nodules larger than 1 cm, determined by ultrasound and thyroid scan appearance (the presence of foci with increased uptake). Before RIT, 54% of patients were pre-treated with anti-thyroid drugs, 11% underwent thyroid surgery and 37% had recurrent hyperthyroidism. In all patients, clinical indications and eligibility for RIT were individually evaluated by a nuclear medicine specialist. Aside from NIH, 9 patients had a comorbid autoimmune disease, including rheumatoid arthritis, pernicious anaemia, and psoriasis and 15 of them had type 2 diabetes. Subjects with known autoimmune thyroid disease and prior or current malignancy were excluded from the study. Patients were divided into 2 groups according to their baseline TPOAb serum level: with normal (below 60 IU/ml) and high TPOAb (above 60 IU/ml).

Patients were categorized as euthyroid or as having developed overt hypothyroidism or subclinical hypothyroidism based on clinical and laboratory values for TSH and thyroxine (FT_4). The euthyroid classification was chosen if the patient's record indicated that TSH and FT_4 levels were within normal ranges, there were no clinical symptoms associated with altered thyroid status, and there was no thyroid replacement medication use. Overt hypothyroidism was designated if the attending physician diagnosed hypothyroidism and supplemental thyroid hormone was used. Subclinical cases were designated if thyroid replacement therapy could not be confirmed but laboratory test showed elevated TSH and normal FT_4 levels.

Assessment of thyroid function

Thyroid function tests, including serum FT_4 (reference range: 10.0–25.0 pmol/L), TSH (reference range: 0.40–4.0 mIU/L), TRAb (normal range, below 1.5 IU/mL), and TPOAb (normal range: below 60 IU/mL), were performed before and 12 months after RIT. TPOAb and FT_4 were assessed by radioimmunoassay. TSH was assessed by immunoradiometric assay (BRAHMS GmbH, Germany).

At baseline and 12 months after RIT all the patients underwent thyroid ultrasonography with the use of a 7.5 MHz transducer. A fine needle diagnostic aspiration biopsy was performed in 23 cases to exclude thyroid malignancy prior to RIT.

RIT procedure

Prior to RIT, all patients underwent a standard assessment of radioiodine uptake after 4, 24 and 48 h, as well as a thyroid scan with ^{131}I after 24 h. Palpable structures were directly mapped on the 1:1 thyroid scan; T½ for radioiodine retention was estimated using radioiodine uptake. The volume of thyroid hot nodules was estimated using a formula for spheres or ellipsoids, or directly from their diameters in the ultrasound scan. The entire thyroid volume was estimated by ultrasonography or planimetric method. The radioiodine dose was calculated from the target thyroid volume, planned dose of absorbed radiation, 24-h thyroid ^{131}I uptake, and the effective half-life of [131]I. Dosimetric data for RIT in the whole group of 100 patients are given in ◉ **Table 1**.

Statistical analysis

Descriptive statistics included frequency distributions (number with condition and percentage) for categorical variables and means, standard deviation (SD), and range for continuous variables. To assess changes from baseline to follow-up, we used a paired t-test or nonparametric Mann-Whitney U-test for continuous variables and Chi-square test with Yates' correction for categorical variables. Statistical analyses were performed using Statistica PL package (StatSoft, Poland).

Results
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Baseline characteristics of the study population are shown in ◉ **Table 2**. Overall, 65% of patients had MNTG and palpable neck mass was found in 88% of them. Recurrence of hyperthyroidism was observed in 37% of patients. There were no significant differences in TRAb, TSH and FT_4 levels between groups with normal and high TPOAb levels. Baseline TPOAb values were significantly higher in subjects with a coexisting non-thyroid autoimmune disease (p=0.041). Prior to RIT, normal thyroid function was found in 36% and hyperthyroidism in 64% of patients. More than 50% of patients received antithyroid therapy before RIT.

One year after RIT, the rates of euthyroidism and hypothyroidism increased (61 and 34%, respectively) (◉ **Table 3**). The prevalence of hypothyroidism was similar in patients with MNTG and TA. Initial thyroid volume, pretreatment with antithyroid drugs, severity of nodular changes/focal lesions in ultrasonography before RIT, total number of recurrences, and radiation dosimetric parameters used for RIT were not associated with the occurrence of hypothyroidism.

Mean values of TPOAb before and after RIT were comparable. However, in the subgroup of patients with normal baseline TPOAb its titres significantly increased after RIT (p=0.030); In subjects with high baseline TPOAb a similar trend was observed but the differences did not reach statistical significance. High TPOAb post RIT was more frequently observed in the group with high baseline titres. Baseline TPOAb did not increase the odds of hypothyroidism after RIT (Odds ratio=1.09; p=0.473). Mean values of TSH, FT_4 and TRAb were comparable in patients with normal and high baseline TPOAb titres.

Discussion
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The concept of this study was based on practical observation that some patients with NIH have an elevated TPOAb level, which may be associated with a higher risk of developing hypothyroidism post RIT [15,16]. We found a 34% prevalence of hypothyroidism at 12 months after RIT which overall is consistent with majority of studies evaluating this therapeutic outcome at a similar time point. High rates of hypothyroidism in NIH treated with RIT were reported both in short- and long-term follow-up. Overall, the rate of hypothyroidism varies from 6 to 55% within the first several years after RIT [15–18]. Predictably,

Table 1 Dosimetric data for radioiodine therapy.

Administered ^{131}I activity (mCi)	18.97 ± 5.63 (9.50–32.8)
Administered ^{131}I activity (MBq)	702 ± 208 (352–1 214)
Thyroid volume (mL)	28.49 ± 16.2 (7.0–90.0)
Absorbed dose (Gy)	250.0 (150.0–400.0)
24-h uptake of [131]I (%)	0.35 ± 0.12 (0.15–0.73)
Effective half-life of [131]I (days)	5.93
	5.20–6.0

Data are means ± SD or medians and ranges

Variables	All (n = 100)	TPOAb below 60 IU/mL (n = 73)	TPOAb above 60 IU/mL (n = 27)	P-value
Age (years)	65.0 ± 11.9	65.43 ± 12.5	63.74 ± 10.5	0.201
Gender (F/M)	83/17	60/13	23/4	0.235
Multinodular toxic goitre (n)	65	49 (67.1%)	16 (59.3%)	0.213
Toxic adenoma (n)	35	24 (32.9%)	11 (40.7%)	0.246
Recurrent hyperthyroidism (n)	37	28 (38.4%)	9 (33.3%)	0.689
Antithyroid drugs (n)	54	40 (54.8%)	14 (51.9%)	0.726
Antithyroid drugs (months)	49.2 ± 60.1	42.3 ± 53.4	55.6 ± 70.0	0.098
Time of withdrawal of antithyroid drugs (months)	2.9 ± 4.5	2.2 ± 4.4	3.3 ± 4.9	0.227
Prior thyroid gland surgery (n)	5	4 (5.5%)	1 (3.7%)	0.308
Palpable neck mass (n)	88	63 (86.3%)	25 (92.5%)	0.402
Hyperthyroidism (n)	64	46 (63.0%)	18 (66.6%)	0.787
Normal thyroid function	36	27 (36.9%)	9 (33.3%)	0.271
Coexisting autoimmune disease (n)	9	5 (6.8%)	4 (14.8%)	0.216
TPOAb (IU/mL)	271.2 ± 1059	34.56 ± 14.2	902.5 ± 1913	0.001
TRAb (IU/mL)	0.402 ± 0.22	0.370 ± 0.24	0.453 ± 0.22	0.172
TSH (mIU/L)	0.61 ± 1.01	0.62 ± 1.08	0.57 ± 0.76	0.199
FT_4 (pmol/L)	15.71 ± 4.73	15.82 ± 4.84	15.60 ± 4.93	0.187

Table 2 Baseline characteristics of the study population.

Data are means ± SD or number (percentage) with condition. P refers to comparison between groups with TPOAb below and above 60 IU/mL

Outcomes at 12 months after RIT	All (n = 100)	Baseline TPOAb below 60 IU/mL	above 60 IU/mL	P-value
Normal thyroid function (n)	61 [a]	45 (61.6%) [b]	16 (59.3%) [b]	0.723
Hyperthyroidism (n)	5 [c]	4 (5.5%) [c]	1 (3.7%) [c]	0.245
Hypothyroidism (n)	34 [c]	22 (30.1%) [c]	12 (44.4%) [c]	0.050
TSH (mIU/L)	2.82 ± 1.2 [c]	3.0 ± 1.27 [c]	2.37 ± 0.95 [c]	0.876
FT_4 (pmol/L)	13.61 ± 4.59	13.56 ± 4.53	13.67 ± 4.61	0.917
TRAb (IU/mL)	0.59 ± 0.6	0.52 ± 0.5	0.61 ± 0.7	0.424
TPOAb (IU/mL)	455.0 ± 1250	55.1 ± 167.7 [a]	1484.6 ± 2066	0.001
TPOAb above IU/mL (n)	32	10	22	0.032

Table 3 Outcomes at 12 months after RIT in patients with high and normal baseline TPOAb.

Data are means ± SD or number (percentage) with condition. P in table refers to comparison between groups with TPOAb below and above 60 IU/ml. [a] P < 0.05; [b] P < 0.01; [c] P < 0.001 vs. baseline category

it has been suggested that the rate of hypothyroidism may be influenced by a high initial size of the thyroid gland [9, 19], prior antithyroid treatment [16], small goiter [9], and a high RAI dose [13]. On the other hand, other studies [17, 20–23], as well as our results, failed to confirm such relationships. Additionally, we found that the rate of hypothyroidism after RIT was not associated with the type of NIH (MNTG or TA), recurrences of hyperthyroidism and severity of nodular changes/focal lesions evaluated in ultrasonography.

It has been reported that pre-existing thyroid autoimmunity may predict the development of hypothyroidism after RIT [13, 15, 16, 22, 23], although other reports including the present study did not support such association [24]. These discrepancies may be partially related to methodological differences between studies. For example, in studies evaluating the outcomes of RIT in NIH, Carceller et al. [15] included several subjects who were TRAb positive at the time of NIH diagnosis, while in the study of Bolusani et al. [16] NIH was diagnosed solely by imaging techniques and baseline TRAb was not measured. This may suggest that in these reports a subset of subjects with coexisting Graves' disease were analysed, while the diagnosis of NIH based on scintigraphic appearance alone may be misleading because the scintigraphic 'hot' area may represent healthy background tissue but infiltrated by lymphocytes [25], as for example in Marine-Lenhard syndrome – a rare variant of Graves' disease with coexistent autonomous thyroid nodules [26, 27]. On the other hand, although we analyzed

only the patients who at baseline were negative for TRAb, this does not exclude autoimmune thyroid disease as probably all patients with this condition have a mixture of different TSH receptor antibodies which possess stimulating (TSAb), blocking (TBAb) or neither stimulating nor blocking (thyrotropin binding immunoglobulins) properties [28].

Aside from these methodological considerations related to diagnosis of NIH, baseline TPOAb level has been reported to predict the development of hypothyroidism after RIT, often with some latency and increasing incidence over time [29, 30]. However, we found that TPOAb was a poor predictor of this condition, similarly as in some other reports [24]. Although we found that the mean TPOAb titer was significantly increased after RIT in the group with its normal baseline level, the rate of hypothyroidism was comparable in patients with normal and high baseline value of this antibody. This may suggest that the occurrence of hypothyroidism might be associated not only with TPOAb performance, but also with RIT-related factors.

The goal of RIT is to destroy thyroid autonomous tissue, which accumulates relatively more radioactive iodine compared to suppressed surrounding tissue. If antithyroid drugs are used prior to ^{131}I treatment, the extranodular (suppressed) tissue is metabolically more active and, as a consequence, it may be irradiated by radioiodine. This may lead to undesired damage of healthy thyroid tissue and hypothyroidism [9, 13, 24]. The latter effect may be overlapped by ionizing radiation-induced the

hibernation-like condition (or prolonged stunning), which temporarily impairs the thyroid function [13, 31]. Additionally, it has also been suggested that autonomously functioning micronodules which may accompany toxic adenoma may degenerate and predispose to impaired thyroid functioning post RIT [32].

On the other hand, in euthyroid or subclinical hyperthyroid patients the protective effect of the functional suppression of the extranodular thyroid tissue by the hyperfunctioning toxic adenoma has been observed [17]. This may lead to a lower iodine uptake of the normal thyroid cells at the time of the ^{131}I administration.

Thus, the patient outcome after RIT represents a net balance between the amount and quality of residual thyroid parenchyma, which may be influenced by antithyroid drugs, thyroid volume, a coexisting thyroid disease [13], and RIT-induced thyroid autoimmunization caused by the release of thyroid antigens [14, 33]. Notwithstanding, as suggested by this study, there is a subset of patients with NIH and elevated baseline TPOAb titers (and possibly other thyroid antibodies) in whom RIT potentially may predispose to hypothyroidism. Hence, it could be speculated that patients with clinically or serologically more pronounced autoimmunity react differently to RIT, compared with patients with less pronounced deterioration of the immune system. This might explain the differences in reported outcomes of RIT in autoimmune and non-autoimmune thyroid hyperthyroidism.

In the current study, 9 % of patients had a coexisting non-thyroid autoimmune disease. These patients had a significantly higher TPOAb level in comparison with those without this coexisting condition. To our best knowledge, there have been no previous reports demonstrating a higher prevalence of autoimmune diseases in patients with NIH. However, the association refers rather exclusively to TPOAb (or possibly also other TSH receptor antibodies) than NIH *per se*, as autoimmune thyroiditis and Graves' disease are often accompanied by production of organ-specific and non-organ-specific antibodies [34, 35].

Limitations of the study

Our study had some limitations. First, due to its observational design, the association between baseline TPOAb and the rate of hypothyroidism at 12 months after RIT may not represent a direct causality, because it may be influenced by several confounding factors known to contribute to the pathogenesis of autoimmune thyroid disease, which were not evaluated in this study. They include serum vitamin D levels, smoking, alcohol consumption, selenium intake, iodine intake, prior infections, parity and estrogen use. Moreover, genetic factors contribute for even 70–80 % to the development of TPOAb and/or TRAb positivity [36]. Therefore, because of the modest sample size and, hence, limited statistical power, we cannot exclude that the differences between patients with high and low baseline TPOAb, which were not adjusted for potential confounders, may be a finding by chance, i. e., a type-1 error.

Second, we used an arbitrary threshold value of 60 IU/ml to define the TPOAb positivity. This value refers to the reference range provided by the manufacturer of radioimmunoassay used in our study and, therefore, it may not apply to other assays. Finally, we demonstrated that baseline TPOAb level did not influence the rate of hypothyroidism at 12 months after RIT. However, the overall prevalence of hypothyroidism progressively increase with time from RIT and, hence, it may be widely varied in different time points of evaluation [16, 17].

In conclusion, 27 % of patients with NIH were positive for TPOAb. However, baseline TPOAb level did not influence the rate of hypothyroidism at 12 months after RIT. Our results suggest a more close surveillance after RIT of patients harboring these antibodies.

Conflict of interest: None.

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